REMARKS

Claims 1, 3-8 and 10-54 are pending in the application. However, claims 25-43 and 48-54 have been withdrawn from consideration by the Examiner. Accordingly, claims 1, 3-8, 10-24 and 44-47 are pending and under consideration in the present application. Claims 1, 10 and 46 are amended herein. Re-examination and reconsideration of the application is requested.

Applicant notes with appreciation the Examiner's indication that the rejections and/or objections not reiterated from previous Office Actions are withdrawn. In the Office Action dated November 19, 2004, none of the rejections or objections made in previous Office Actions were reiterated. However, several new grounds of rejection were presented. As discussed in the following remarks, Applicant respectfully traverses each of the new grounds of rejection and requests re-examination and reconsideration of the application and claims.

Response To Rejections Under 35 U.S.C. 112, Second Paragraph:

Claims 10-18 were rejected under 35 U.S.C. 112, second paragraph, as being dependent upon a claim that has been cancelled. In response, claim 10 is amended herein to depend from claim 3. As claim 3 is pending and under consideration in the present application, it is respectfully submitted that the rejection of claims 10-18 is traversed. Consideration and examination of claims 10-18 is requested.

In addition, claims 1, 3-8, 19-24, 44, 46 and 47 were rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, where such omission amounts to a gap between steps. The Examiner stated that the omitted steps are "steps of isolating the enzyme." The Examiner further stated that, without that step, it is unclear from the claims and specification how one of ordinary skill in the art can measure the concentration of glucose oxidase in order to determine if the colonies contain active glucose oxidase.

Applicant respectfully submits that a step of isolating the enzyme is not an omitted esstential step of the claimed method of claims 1, 3-8, 19-24 and 44. Accordingly, the rejection of those claims under 35 U.S.C. 112, second paragraph, is respectfully traversed. With regard to

claims 46 and 47, applicant submits that those claims, as amended herein, are in compliance with 35 U.S.C. 112, second paragraph.

More specifically, claim 1 is directed to a method for *formulating* an enzyme. After the enzyme is formulated (and colonies are screened for the enzyme and desired peroxide resistant properties), the enzyme may be isolated and concentrated and placed into a sensor. (See page 13, lines 2-10 of the present specification) However, for at least some embodiments of *formulating* the enzyme, it is not necessary that the enzyme be isolated, concentrated or placed into a sensor to have been formulated.

The present specification describes various embodiments of formulating an enzyme, including screening the enzyme to assess its functionality. While in one embodiment, such assessment may include sufficiently isolating and concentrating the enzyme, placing the enzyme in a sensor and testing the functionality of the sensor, other embodiments described in the specification may employ an assay which tests the production of peroxide generated by glucose oxidase reating with glucose and yet other embodiments may employ a test for fluorescence. (See page 10, line 16 to page 11, line 6.) Testing for active glucose oxidase in these or other manners may be performed after incubating active colonies in peroxide to identify colonies with a desired peroxide resistance properties. (See page 12, lines 1-5 of the present specification.) In this manner, concentrations of glucose oxidase may be measured by measuring the active glucose oxidase after incubation in peroxide for defined periods.

Thus, the patent specification describes embodiments in which an enzyme may be forumulated (including screened) without requiring the enzyme to be isolated, concentrated and placed in a sensor. In that regard, the rejection of claims 1, 3-8, 19-24 and 44 under 35 U.S.C. 112, second paragraph, as omitting an essential step is respectfully traversed.

It is noted that dependent claims 46 and 47 recite placing the enzyme in a sensor. Accordingly, claim 46 is amended herein to further include "isolating the glucose oxidase." The rejection of claims 46 and 47, as amended herein, is respectfully traversed.

Claims 1, 3-8, 19 and 44-47 were further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner stated:

> "The claims are drawn to a method of generating a library of mutated glucose oxidase genes. There is no reference to any of type of mutation until claim 31. Depending on the type of mutagenesis employed, the resulting mutants will vary greatly. Therefore, the claims have been interpreted broadly."

This rejection is respectfully traversed. The claims under consideration are directed to "a method of formulating an enzyme," as recited in the preamble of claim 1. While a part of claim 1 is "creating a library of mutated glucose oxidase genes," the claim involves several additional parts, including growing colonies and screening colonies by determining whether the colonies contain active glucose oxidase and determining whether the colonies have peroxide resistance properties. Thus, the claims are not drawn to a method of generating a library of mutated glucose oxidase genes, but, instead, are directed to a method of formulating an enzyme (which includes, as one of several parts, creating a library of mutated glucose oxidase genes).

The Examiner's citation of claim 31 as being a first reference to any type of mutation is not understood. Furthermore, it is respectfully submitted that claim 1 does specify a type of mutation to which the screening relates – peroxide resistant mutations of glucose oxidase. In particular, lines 9 and 10 of claim 1 recite that screening of the colonies is accomplished by determining whether the colonies contain active glucose oxidase and determining whether the colonies have peroxide resistance. Thus, while mutations within the created library of mutated glucose oxidase genes may vary among the genes in the mutated gene library, claim 1 further specfies using those genes for growing colonies and screening the colonies for desirable properties (existence of active glucose oxidase and peroxide resistance). Inherent in a screening function is *screening out* those colonies that do not have the desired properties, leaving colonies containing glucose oxidase enzyme having desired peroxide resistant properties. Thus, it is respectfully submitted that claim 1 is sufficiently definite with respect to the type of mutation of glucose oxidase (mutation that provides a desired peroxide resistance property) and is, therefore,

in compliance with the requirements of 35 U.S.C. 112, second paragraph. Dependent claims 3-8, 19 and 44-47 are also similarly definite with respect to the type of mutation.

Claims 1, 3-8, 19-24 and 44-47 are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that the claims recte the term "gene," but the "metes and bounds of the phrase in the context of the claims is not clear to the Examiner. The Examiner states:

> "A gene comprises of a coding sequence and itrons, exons and regulatory sequences. A perusal of the specification did not provide the Examiner with a specific definition for the above phrase. Therefore, it is not clear whether the above term in said claims encompass the intronic and regulatory sequences or is limited to a cDNA."

This rejection is also respectfully traversed in that the claimed method would be readily understood and specific to one of ordinary skill in the art as including any glucose oxidase gene, whether having introns, exons or both. Embodiments of the claimed method may be employed to formulate an enzyme having peroxide resistant properties, regardless of the type of glucose oxidase genes employed in the library. Once enzymes are formulated according to embodiments of the present invention (including screened for desired peroxide resistance), the enzymes may be tested, if desired, for introns, exons, or the like. However, such is not necessary to formulate the peroxide resistant enzyme according to embodiments of the present invention.

Claims 1, 3-8, 19-24 and 44-47 are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that the phrase "colonies have peroxide resistant properties" is unclear.

This rejection is respectfully traversed, in that one of ordinary skill in the art would understand the cited phrase in the context of the claimed invention. Moreover, it is noted that the cited phrase has been in the claims from the start of prosecution of the present application, where such claims have been previously examined in previous Office Action and were not rejected as

being indefinite. However, to expedite prosecution, the claims are amended herein to recite "determining whether the colonies have desired peroxide resistant properties."

Examples of making such a determination is described in the patent specification, with respect to embodiments in which colonies are screened for active glucose oxidase, after the colonies have been incubated in peroxide (or peroxide introduced in other manners). As described in the patent specification, "colonies that still have active glucose oxidase, after being incubated in peroxide, may exhibit a desirable peroxide-resistive characteristic." (See page 12, lines 1-12 of the present specification.) One of ordinary skill in the art would be able to define desired peroxide resistance properties and employ embodiments of the present invention to formulate enzymes and determine which colonies have a desirable peroxide resistance properties. A desired resistance may be, for example, a resistance to a peroxide incubation process or other form of introduction of peroxide to a colony. Accordingly, the rejection of claims 1, 3-8, 19-24 and 44-47 are further rejected under 35 U.S.C. 112, second paragraph, is respectfully traversed.

Response To Rejection Under 35 U.S.C. 103(a)

Claims 1, 3-5, 8, 19-24 and 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valdes et al. and Current Protocols in Molecular Biology. This rejection is respectfully traversed.

In particular, neither Valdes et al. nor the Current Protocols in Molecular Biology reference describe or suggest formulating a glucose oxidase enzyme by mutating glucose oxidases to make them resistant to peroxide degredation. Moreover, one of ordinary skill in the art would not have been led by the prior art of record to mutate glucose oxidase genes, much less to mutate such genes and screen for desired peroxide resistance properties. Such procedures would have been a drastic departure from the state of the art and, without the benefit of the present specification as a guide, would not have been obvious to one of ordinary skill in the art.

The Examiner argues that Valdes et al. teach that glucose oxidases in glucose sensors degrade over time due to hydrogen peroxide. Without refering to any disclosure or suggestion in the prior art, the Examiner then argues that "one of ordinary skill in the art would recognize usefulness of mutant glucose oxidases that are resistant to peroxide degredation and thereby

generate such mutants with recombinant skills well known in the art." (Office Action, page 6, lines 4-8.) However, Valdes et al. provides no suggestion or motivation to mutate glucose oxidases to make them resistant to peroxide degredation. Instead, Valdes et al. only discusses the degredation effects of peroxide on glucose oxidase. Valdes et al. makes no attempt to solve the problem.

One of ordinary skill in the art, without the benefit of the present specification, would not have found any teaching or suggestion in Valdes et al. and would not have been otherwise motivated to mutate glucose oxidase and screen mutated glucose oxidase for peroxide resistance properties. It is improper to employ the benefit of Applicant's own specification to embelesh upon the teachings of the prior art. Valdes et al. provides no suggestion of addressing the degratory effects of peroxide on glucose oxidase. As such, one of ordinary skill in the art would have considered other, well-known techniques for addressing the peroxide degredation noted by Valdes et al., including processes for removing or neutralizing peroxide without changing he glucose oxidase (such as by adding an antioxidant or peroxidase to the glucose oxidase to break down peroxide or by coating the glucose oxidase enzyme with a protective coating), such as described in U.S. Patent No. 6,689,265 to Heller et al. and the article titled "Glucose ENFET doped with MnO_2 powder" by Yin et al (copies enclosed).

In particular, the direction taken by those skilled in the art for addressing the peroxide degredation of glucose oxidase is wholly different from the direction of the present invention. In U.S. Patent No. 6,689,265 to Heller et al., a peroxide generating enzyme may include a sufficiently thick, natural, electrically insulating protein or glycoprotein layer. (See column 6, lines 59-67 of the Heller et al. patent.) Heller et al. also disclose an alternative embodiment in which a peroxide generating enzyme is immobilized in a non-conducting inorganic or organic polymeric matrix. (See column 7, lines 3-11 of the Heller et al. patent.) Also, Heller et al. describe a first layer enzyme 11 (peroxidase) that reduces peroxide generated from a second layer (glucose oxidase layer) 13. The Yin et al. article describes the addition of MnO2 to catalyse peroxide and produce water and oxygen therefrom. Thus, both the Heller et al. patent and the Yin et al. article show that the direction taken by those skilled in the art is to provide additives or complex multi-layer sensor structures to remove hydrogen peroxide. These references show that

those skilled in the art were not considering mutating glucose oxidase genes and growing and screening colonies for peroxide resistance, but instead had attempted to address the peroxide production issue by removing or neutralizing peroxide (not by altering the glucose oxidase).

While the Examiner has cited the Current Protocols in Molecular Biology reference as teaching methods for generating random mutagenesis via PCR and screening for mutants having desired properties, the cited reference provides no teaching or suggestion of creating a library of mutated glucose oxidase genes and of screening colonies for peroxide resistant properties. The Examiner cited the Valdes et al. reference for a teaching of degredation effects of peroxide on glucose oxidase. However, as noted above, Valdes et al. does not teach or suggest any resolution of such effects, much less a teaching or suggestion to employ a mutation process such as described in the Current Protocols in Molecular Biology reference. Furthermore, the Current Protocols in Molecular Biology reference also provides no teaching or suggestion of mutating glucose oxidase genes, much less of screening colonies of glucose oxidase for peroxide resistance.

Without the present disclosure as a guide, one of ordinary skill in the art would not have found Valdes et al.'s discussion of the degradation of glucose oxidase as a prompt or suggestion to employ a mutation process as described in the Current Protocols in Molecular Biology reference to mutate glucose oxidase genes. Instead, as noted above, one of ordinary skill in the art would have looked to conventional manners of removing peroxide, such as additives for removing or neutralizing peroxide. Accordingly, the rejection of 1, 3-5, 8, 19-24 and 44-47 under 35 U.S.C. 103(a) is respectfully traversed.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatatable over Valdes et al., Wohlfahrt et al. and Current Protocols in Molecular Biology and further in view of Byalina et al. This rejection is respectfully traversed, at least for reasons as discussed above with regard to independent claim 1.

In particular, claims 6 and 7 are dependent (directly and indirectly) on claim 1. Due to their dependencies, the distinctions over the prior art of record discussed above with respect to claim 1 apply to claims 6 and 7, as well. Moreover, it is noted that the Wohlfahrt et al. reference

and the Byalina et al. reference, alone or in combination, do not address the distinctions over the references discussed above with respect to claim 1. Neither of those references (alone or combined with other references cited in the rejection) teach or suggest mutating glucose oxidase genes or of screening colonies of glucose oxidase for peroxide resistance.

The Bylina et al. reference was cited by the Examiner for a discussion of screening assays of colonies containing mutant proteins. However, Bylina et al. does not teach or suggest mutating glucose oxidase genes, screening colonies for peroxide resistance or other aspects of the claimed method for formulating an enzyme. Thus, Bylina does not address the distinctions noted above.

While no specific portions of the lengthy Wohlfarht et al. reference was cited in the rejection, the portions of the Wohlfahrt et al. reference previously cited by the Examiner describe modeling glucose oxidase, but do not appear to describe or suggest any manner of addressing peroxide inactivation of glucose oxidase. Instead, Wohlfahrt et al. describe very different processes involving relatively complex modeling and simulations of specific enzymes. The directions taken by Wohlfahrt et al. and other references of record and the lack of action taken by others shows that the above-discussed references were not focused in the direction of the present invention and, instead, were focused in other directions. Thus, the cited references, alone or in combination, would not have led one of ordinary skill in the art to the claimed invention. Therefore, the rejection of claims 6 and 7 is respectfully traversed.

The method recited in the pending claims of the present application can provide significant advantages over the prior art of record. The ability to form a stable enzyme which is peroxide resistant and which may be employed in an altered environment (oxygen free environment), such as a biosensor, can provide significant advantages in extending the life of biosensors. When used in an implanted medical device (such as an implanted blood glucose sensor), peroxide resistance and, thus, a capability for extending the life of the enzyme can provide considerable patient comfort and safety advances, for example, by reducing the frequency of surgical sensor replacements. Moreover, the ability to form enzymes with peroxide resistant properties suitable for biosensor applications in a relatively inexpensive, non-complicated and reliable process can provide significant advantages with respect to the ability to

manufacture readily available supplies of the enzyme and, thus, increasing the availability of longer-life biosensors to more patients.

Had the presently claimed method been obvious over the prior art of record, then such significant advantages would have led the authors of those prior art references to at least mention the possibility of performing such methods. However, no such disclosures were made in the cited references. Thus, the significant advantages available with the present invention, as compared to the processes described in the prior art of record, shows that the presently claimed invention is not obvious over the prior art of record. Accordingly, the rejections of claims 1, 3-8, 10-24 and 44-47 are respectfully traversed.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: April 19, 2005

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